REMARKS

Claims 18, 19, 22, 23, 28-33, and 35-44 were pending in the instant application. Claims 18, 19, 22, 23, 28-33, and 35-44 have been cancelled and new claims 45-57 have been added. Support for the new claims can be found throughout the specification and examples, and in the claims as previously pending. New claims 45-54 are identical to claims 1-10 as issued in the corresponding European Patent (EP 0 974 052 B1). Applicant reserves the right to pursue the subject matter of the cancelled claims in this or another application. No new matter has been added.

Rejection of Claims 18, 19, 22, 23, 26, 28-33 and 35-44 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 18, 19, 22, 23, 26, 28-33 and 35-44 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which is regarded as the invention.

Specifically, the Examiner objects to terms such as "substantially changed affinity", "similar", "substantially fails", "similar activity", "substantial reduction in activity", "normal function", etc. Applicants traverse this rejection for the following reasons.

The MPEP states "piecemeal examination should be avoided as much as possible" (see MPEP §707.07(g)). The instant application has been pending for nearly seven years and Applicants have received and responded to a number of office actions. Despite the extensive prosecution of this application, the Examiner raises the foregoing 112, second paragraph rejection for the first time in the instant office action. The rejection of the pending claims over language that has been present since the filing of the application is unfair to Applicants and contrary to Patent Office policy.

While in no way acquiescing to the validity of the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended the claims by introducing the claims as allowed in Europe. These claims eliminate a number of the terms that the Examiner has objected to, thereby rendering this rejection moot as it pertains to those terms.

Moreover, the remaining terms that the Examiner has objected to are terms that are common and well known in the English language and provide a clear and definite

meaning to one of ordinary skill in the art. A search of issued claims in United States patents reveals thousands of issued claims which use the terms which the Examiner has objected to. Moreover, to this point in prosecution, the Examiner of the instant application also found these terms to meet the requirements of section 112, second paragraph. Similarly, the European Patent Office has found the terms to be clear and definite (see European Patent 0 974 052 B1).

The Examiner further objects to a number of claims over the use of the terms "operational activity", "operates", and "operate in a manner similar to". For the reasons indicated above and for the reasons of record Applicants respectfully traverse this rejection. For the Examiner's convenience enclosed are copies of the four abstracts originally filed with the Response to Office Action filed April 5, 2001.

Claim 44 has been cancelled, thereby rendering the rejection of this claim due to a lack of method step moot.

The Examiner has further rejected claims over the use of the terms "gene" and "cell". Specifically, the Examiner states that the claims are indefinite because the gene or cell can refer to any gene or any cell in any mammal. Applicant traverse this rejection. It appears as though the Examiner is indicating that a specific gene or cell must be specified to meet the requirements of section 112, second paragraph. This requirement is unreasonable and incorrect. The instant invention provides a general method of screening for modulators of aberrant proteins, e.g., receptors. To require the limitation to a specific receptor would unfairly restrict the applicants invention. The ordinary skilled artisan clearly understands the meaning of the terms cell and gene and would find the claims to be clear and definite.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 18, 19, 22, 23, 26, 28-33 and 35-44 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 18, 19, 22, 23, 26, 28-33 and 35-44 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. The Examiner is of the opinion that the specification is enabled for methods of

screening for a substance that restores the normal function of the β3 adrenergic receptor, but not for methods for screening for a substance that restores normal function to any mutant gene. Applicant respectfully traverse this rejection.

Applicants have amended the claims so that the broadest claim (claim 45) no longer indicates that the compound is for the use in the treatment of a disease. Rather the instant claims are directed to a screening method for substances capable of operating an aberrant receptor.

As the Examiner is aware, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Clearly, identifying receptors that have a mutation in the structural gene which results in substantially changed affinity for the natural ligand would require no more than routine experimentation for one of ordinary skill in the art. Once an aberrant receptor is identified, the ordinary skilled artisan could screen for substances capable of operating the aberrant receptor using the teachings provided in the specification.

Applicants specification sets forth detailed teachings that would allow one of ordinary skill in the art to practice the claimed screening methods. For example, the specification teaches how one of skill in the art would express and isolate an aberrant gene product (see, for example, page 21, line 13 through page 26, line 17). Applicants' specification further teaches how one would screen compounds for the ability to operate the aberrant receptor (see, for example, page 27, line 24 through page 30, line 16). Moreover, Applicants provide an exemplary aberrant receptor, β 3 adrenergic receptor, in the Examples section and describe assays that were used to determine the activity of the receptor in the presence of candidate substances (see Examples 1-6). Applicants further provide a working example of a screening assay of the invention (see Example 7 in which compounds were screened for the ability to modulate the Trp64Arg β3 adrenergic receptor). Accordingly, based on the extensive teachings in the specification and the working examples, one of ordinary skill in the art would be able to practice the claimed methods to screen compounds for their ability to modulate aberrant receptors.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 18, 19, 22, 23, 26, 28-33 and 35-44 Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 18, 19, 22, 23, 26, and 28-44 under 35 U.S.C. §103(a) as being obvious over Lebrun et al., or Birnbaumer et al., or Green at al, or Kong et al, in view of Choong et al., and further in view of Dower et al., all previously of record. Applicant respectfully traverses this rejection for the reasons previously of record and for the reasons set forth below.

In view of the amendments to the claims, Applicants maintain that no reasonable combination of any or all of the references of record discloses or suggests the claimed subject matter of the present claims. In order to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), ***every element*** of the claim under scrutiny must be disclosed or suggested in the cited references in such a manner that the proposed combination of teachings of the different references would have been suggested to one of ordinary skill in the art.

The instant claims are directed to methods of screening for a substance capable of operating an aberrant receptor being a receptor with a mutation in the structural gene resulting in substantially changed affinity for the natural ligand. Applicants maintain that the primary reference, Lebrun et al., does not teach or suggest mutant receptors having substantially changed affinity for their natural substrate. The binding affinity of the Val^{382} insulin receptor used by Lebrun et al. was entirely normal as indicated on page 11276, right column, fourth paragraph.

The Examiner indicates that the requirement that the aberrant receptor have substantially changed affinity is stated in the preamble and terms are poorly defined are used. While in no way acquiescing to the Examiner's rejection, the preamble has been amended to remove some of the objected to terms. The term "substantially changed" is clear and definite as previously indicated.

Moreover, Applicants respectfully disagree with the Examiners' assertion that preamble is not given patentable weight. In addition to the reasons of record, Applicants ask the Examiner to consider MPEP § 2111.02. In *Corning Glass Works* the court held that any terminology in the preamble that limits the structure of the clamed invention must be treated as a claim limitation. Specifically, the court stated that "the determination of whether preamble recitations are structural limitations can be resolved only on review of the entirety of the application 'to gain an understanding of what the inventors actually invented and intended to encompass in the claims'". *Corning Glass Works* v. *Sumitomo Elec.U.S.A., Inc.* 868 F.2d 1251, 1257, 9 USPQ2d, 1962, 1966 (Fed. Cir. 1989). Clearly, a reading of the specification as filed indicates that the entire invention is directed to screening molecules for the ability to operate aberrant gene products. Accordingly, the limitation in the preamble that the receptor is an aberrant receptor with a mutation in the structural gene resulting in substantially changed affinity for the natural ligand should be read as a structural limitation to the claim.

Moreover, Lebrun et al. does not in fact teach any 'screening assays', as this term is understood in the context of the pending claims. The goal of Lebrun et al. was to study a particular mutation (Val^{382}) and how it affected the function of the insulin receptor. Specifically, Lebrun et al. was attempting to study the role of conformational

change in insulin receptor activation. Lebrun et al. was purely a mechanistic study, and not a screening assay for compounds that could activate the mutant receptor.

Based on the foregoing, it is clear that Lebrun et al. does not teach the use of a aberrant receptor as specified in the instant claims.

Moreover, for the reasons of record, none of the remaining references make up for this deficiency in Lebrun et al. and, therefore, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

REMARKS

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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11: Brain Res Mol Brain Res 2000 Dec 28;85(1-2):209-17

Distribution of dopamine D1 receptors in the nucleus paraventricularis of the hypothalamus in rats: an immunohistochemical study.

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The present study investigated the distribution of dopamine D1 receptor protein in the nucleus paraventricularis of the hypothalamus. It was found that the nucleus paraventricularis of the hypothalamus contains a relatively large number of cells which are positive for presence of dopamine D1 receptor protein. The vast majority of dopamine D1 receptor-positive neurons was found in the magnocellular part, but they were also present in considerable quantity in the parvocellular part of this subregion of the hypothalamus. When measured by the Western blot technique, the quantity of D1 receptor protein found in the paraventricular nucleus of the hypothalamus was at the level found in the prefrontal cortex. It was also found that dopamine D1 receptor protein was present in neurons constitutively displaying phosphorylated CREB protein, i.e. neurons which are, as might be speculated, under the tonic influence of neurotransmitters whose receptors operate via cAMP and pCREB as second or third messengers. The presence of dopamine D1 receptors in the nucleus paraventricularis of the hypothalamus may suggest, at an anatomical level, that these receptors are involved in controlling the release of hormones, as well as their synthesis at the level of transcription, which is regulated by phosphorylation of CREB protein. Finally, the present immunocytochemical findings offer an anatomical substrate for the role of dopamine and its receptors of D1 subtype in the regulation of the activity of paraventricular

neurons seen in the functional studies.

7: J Pharmacol Exp Ther 2000 Dec;295(3):1031-42

Dose- and time-dependent bimodal effects of kappa-opioid agonists on locomotor activity in mice.

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The kappa-opioid agonists U50488H, bremazocine, and BRL52537, and the mu-opioid agonist morphine were compared in their ability to modify spontaneous motor activity in male NMRI mice. Higher, analgesic doses of the kappa-agonists reduced rearing, motility, and locomotion in nonhabituated mice. These effects, as well as the analgesic action of U50488H, were blocked by the selective kappa-opioid antagonists nor-binaltorphimine and DIPPA. In contrast, lower, subanalgesic doses (1.25 and 2.5 mg/kg for U50488H; 0.15 and 0.075 mg/kg for bremazocine, and 0.1 mg/kg for BRL52537) time dependently increased motor activity. The stimulatory effects of U50488H and bremazocine were not observed in habituated animals and were reduced by dopamine depletion. Surprisingly, the stimulatory effects of U50488H and bremazocine were not blocked by nor-binaltorphimine and DIPPA but they were completely eliminated by naloxone (0.1 mg/kg). The effects of morphine were dose-dependent; an initial limited suppression was followed by increased motility and locomotion (but not rearing) with a peak effect at 20 mg/kg both in habituated and nonhabituated mice. The selective mu-opioid antagonist beta-funaltrexamine blocked morphine-induced motor stimulation and analgesia but failed to affect the analgesic and motor stimulatory effects of U50488H. The results indicate that kappa-opioid agonists interact with different functional subtypes of opioid receptors. A stimulatory, naloxone-sensitive but nor-binaltorphimine- and DIPPA-insensitive subtype of opioid

receptor appears to operate only when the dopamine system is tonically active in nonhabituated animals. At higher doses, kappa-agonists produce analgesia and motor suppression, effects mediated by a "classic" (inhibitory) kappa-opioid receptor.

45: Am J Physiol Heart Circ Physiol 2000 Jun;278(6):H2057-68

Differential role of ionotropic glutamatergic mechanisms in responses to NTS P(2x) and A(2a) receptor stimulation.

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Activation of ATP P(2x) receptors in the subpostremal nucleus tractus solitarii (NTS) via microinjection of alpha,beta-methylene ATP (alpha,beta-MeATP) elicits fast initial depressor and sympathoinhibitory responses that are followed by slow, long-lasting inhibitory effects. Activation of NTS adenosine A(2a) receptors via microinjection of CGS-21680 elicits slow, long-lasting decreases in arterial pressure and renal sympathetic nerve activity (RSNA) and an increase in preganglionic adrenal sympathetic nerve activity (pre-ASNA). Both P(2x) and A(2a) receptors may operate via modulation of glutamate release from central neurons. We investigated whether intact glutamatergic transmission is necessary to mediate the responses to NTS P(2x) and A(2a) receptor stimulation. The hemodynamic and neural (RSNA and pre-ASNA) responses to microinjections of alpha,beta-MeATP (25 pmol/50 nl) and CGS-21680 (20 pmol/50 nl) were compared before and after pretreatment with kynurenate sodium (KYN; 4.4 nmol/100 nl) in chloralose-urethan-anesthetized male Sprague-Dawley rats. KYN virtually abolished the fast responses to alpha,beta-MeATP and tended to enhance the slow component of the neural responses. The depressor responses to CGS-21680 were mostly preserved after pretreatment with KYN, although the increase in pre-ASNA was reduced by one-half following the glutamatergic blockade. We conclude that the fast responses to stimulation of NTS P(2x) receptors are mediated via glutamatergic ionotropic mechanisms, whereas the slow responses to stimulation of NTS P(2x) and A(2a)

receptors are mediated mostly via other neuromodulatory mechanisms.

60: Oncogene 2000 Mar 2;19(10):1354-61

Two mutations affecting conserved residues in the Met receptor operate via different mechanisms.

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We have investigated the mechanism by which two oncogenic mutations (M1268T and D1246H/N; Amino-acids are numbered according to Schmidt et al., 1999) affecting conserved residues in the catalytic domain of the Met receptor, activate its transforming potential. Both mutations were previously found in tumorigenic forms of the Ret and Kit receptors, respectively. The mutated residues are located either in the P+1 loop (M) or within the activation loop (A-loop) (D), which in a number of receptor tyrosine kinases harbors a pair of tandem tyrosines (Y1252-1253 in Met). Ligand-induced dimerization promotes their phosphorylation, and locks the A-loop into an open conformation. When unphosphorylated, the tandem tyrosines inhibit enzymatic activity by blocking the active site. Upon Y-->F mutation of Y1252-1253, neither ligand binding nor Tpr-mediated dimerization can release this block. Here we show that the M1268T mutation partially rescues the kinase activity (and the transforming ability) of the Y1252-1253F Tpr-Met mutant, but is completely dependent on dimerization for its effect. In contrast, the two D1246H/N mutants strictly depend on Y1252-1253 for activity. Surprisingly, however, they constitutively activate the isolated cytoplasmic TK domain of Met (Cyto-Met). These data indicate that the two mutations operate via distinct mechanisms.